# KwaZulu-Natal Epidemiology Bulletin

**Issue 15**

## Surveillance of XDR and MDR at COSH, 2005-2006

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**March 2007**

Published by:
The Epidemiology Unit
KwaZulu-Natal Department of Health
Private Bag X9051
Pietermaritzburg 3200

This issue has been sponsored by the Italian Co-operation

# EDITORIAL

KwaZulu-Natal Province has been heavily impacted by the interconnected epidemics of TB and HIV/AIDS. The provincial rates of both are among the highest in Southern Africa. During the past few years, it has become apparent that a substantial and growing threat of drug resistant TB has emerged, further complicating and compromising the diagnosis, treatment and outcomes of patients who are co- infected with TB and HIV.

Epidemiologic and clinical data has focused attention on Tugela Ferry in the Msinga District of KwaZulu-Natal, where large numbers of patients with multiple drug resistant (MDR) and extensively drug resistant (XDR) TB have been described and characterized. MDR TB is defined as resistance to isoniazid and rifampin and XDR TB as resistance to these first line drugs as well as second line drug resistance to at least fluoroquinolones and one injectable agent- capreomycin and/or aminoglycosides (kanamycin or amikacin). Both MDR and XDR TB have been known to be present in the province since 2001, but the magnitude of the problem and its dangerous consequences have only been recently appreciated. In addition, the KZN strain of M. Tuberculosis, present in most of the Tugela Ferry cases, has been known since 1995. The salient characteristics of the cases in Tugela Ferry included: HIV co infection in all tested, recent transmission (likely both nosocomial and community spread) and rapid and extremely high levels of mortality. Indeed, many cases were recognized post mortem, as the cultures identifying the presence of XDR TB returned after patients had expired.

The collision of drug resistant TB and HIV disease is not unique to KwaZulu-Natal. In the early days of the HIV/AIDS epidemic in industrialized countries, similar events were described and eventually subsided. But the magnitude of both the TB and HIV epidemics in Southern Africa make this much less likely. Indeed, although multifactorial in origin, it is the high prevalence of HIV infection and the enormous subsequent strain placed on the TB programs that have been most responsible for generating this disastrous situation. It would be dangerous and wishful thinking to expect that this problem will disappear. Rather, intensive effort is required to confront it in an organized and determined way. Fortunately, such effort is now being mounted on a province wide scale.

First, it is essential to rapidly and fully characterize the epidemiology of MDR and XDR TB in the province and beyond. Preliminary information makes it clear that these organisms are not confined to Tugela Ferry, but are widely distributed in the province and present in all other provinces in South Africa as well. Without knowing the extent and location of the problem, targeted as well as general interventions will not be possible.

Second, the TB programs must be strengthened with additional resources, personnel, facilities and expertise. It is not possible to address this situation without rapid escalation in all of these areas.

Third, increased attention must be paid to infection control policies and practices within health care facilities to reduce the risk of transmission to susceptible patients and staff. Simple

measures like enhancing natural ventilation and provision of respirator masks and more complex provision of air borne infection isolation facilities widely distributed in the province are essential-and activity in all of these areas is necessary and moving forward.

Fourth, treatment for drug resistant TB must be made more widely available in the province. Both the drugs themselves and the expertise to administer them safely and effectively in multiple sites in the province are necessary as the problem continue to grow. More widespread treatment has two complimentary benefits-it offers benefit and hope to those who are so infected and second, it provides the chance of reducing transmission of drug resistant organisms to others.

Fifth, expansion of existing TB diagnostic facilities for culture and drug sensitivity testing is needed immediately as is the development and deployment of more rapid TB diagnostics, so that both TB and drug resistance can be identified sooner and both therapeutic and preventive measures instituted. The availability of the provincial TB reference laboratory at Inkosi Albert Luthuli hospital has been critical in defining the current knowledge about XDR TB in the province, a resource not available in most other locations in South Africa and lacking Africa as a whole.

Sixth, the antiretroviral roll out must continue to accelerate, as treatment for HIV/AIDS is associated with diminished risk of TB reactivation, transmission to others and TB disease progression. The need to identify TB cases within HIV programs and HIV among those with TB has never been greater and illustrates the obvious but difficult to implement need for more coordination and integration between TB and HIV programs.

Finally, recognition must be given to the wide array and huge number of health care workers at all levels in the province who are standing their ground and doing their best for the benefit of their patients and the community during this most difficult of times.

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## ACRONYMS & DEFINITION OF TERMS

| | |
|---|---|
| ARV | Antiretroviral therapy |
| COSH | Church of Scotland Hospital |
| DOH | Department of Health |
| DOT | Direct Observed Treatment |
| Epidemic | Significant increase in the number of cases compared to seasonal fluctuations |
| KZN | KwaZulu-Natal |
| MDR | Multiple Drug Resistance to Isoniazide & Rifampicin |
| Outbreak | A significant increase in the number of cases that is limited in time and place (e.g. closed institution) |
| OPD | Outpatients |
| XDR | Extremely Drug Resistance to Isoniazid & Rifampicin and at least two second line antibiotics, which at COSH were Kanamycin & Ciprofloxacin |
| TB | Tuberculosis |


## Acknowledgment

Dr Venanzio Vella, Italian Cooperation, DOH/KZN, analysed the data and wrote the report, which would not have been possible without the contribution of many people. The Italian Cooperation (IC) financed the surveillance system through its direct channels and through the Italian National Institute of Health. The staff at Church of Scotland Hospital had been the primary driving force behind the organization of the data gathering. The district level provided the tracing teams which agreed to add the extra task of taking the GPS coordinates. The diagnostic results of the culture specimens were carried out by the provincial laboratory at the Albert Luthuli. The GIS and Data Management Unit/DOH provided the GPS and produced the map. King George provided the data on the cases that were referred from COSH.

## Abstract

This Issue of the Epidemiology Bulletin provides an update on the multidrug resistant (MDR) and extremely drug resistant (XDR) TB at Church of Scotland Hospital (COSH) between 2005 and 2006. The Italian Cooperation provided technical assistance to COSH since October 2006 to assess the different data sources that were used to record MDR, XDR and contacts. The GIS Unit of the DOH provided the GPS to the tracing teams and mapped the cases. This allowed to describe the epidemic in place and time and to set up the next steps to improve the surveillance system. The surveillance should not be limited to update the number of cases according to standardized data collection but it should monitor the feasibility, cost and effectiveness of the containment strategies. The surveillance should be expanded in scope to include process and outcome indicators of the whole TB programme to improve its effectiveness in preventing the development of further antibiotic resistance.

A total of 180 MDR and 221 XDR cases were diagnosed between 1/1/05 and 31/12/06 mainly related to inpatients. That these numbers reflected the situation among inpatients was confirmed by the fact that both the MDR and XDR cases increased in winter and decreased in summer. Harsher winter conditions increase morbidity for respiratory infections overall, leading to higher hospitalization in winter and therefore a higher chance of being diagnosed. Crowded conditions and less ventilation are also likely to have increased intra-hospital transmission in the colder season.

The situation found at COSH is likely to represent the tip of the iceberg. The other hospitals have continued to follow passive detection by collecting specimens according to the TB control guidelines. This allowed to capturing a much lower number of cases compared to COSH where all inpatients of the TB wards are being tested. Recently, the TB programme has conducted a point prevalence survey in a few hospitals by sampling suspect TB cases among the OPD patients. However, the prevalence of XDR in this group is likely to be so low that the sample size might not have had the power to estimate it, leading also in this case to under-estimation.

It is critical to expand the surveillance to the other three district hospitals of Umzinytahi by applying the same inclusion criteria used at COSH. Although the systematic selection of inpatients in the TB wards would not provide population estimates, nonetheless it will produce comparable trends in the most at risk population in a whole district. The trends in the estimates of MDR and XDR in the hospitalized population will then be used as a proxy of effectiveness of the containment strategies.

The XDR epidemic is the likely result of poor compliance with treatment protocols. The first point to be clarified is that rifampicin and isoniazid (first line drugs) are specifically used for TB. This makes MDR a proxy of poor compliance to TB treatment protocols of first line drugs. The extra resistance to kanamycin and ciprofloxacin is a less specific proxy of what is going on in the TB programme because these antibiotics are used for other infectious diseases. For example, the resistance of gonorrhea to ciprofloxacin has been known since the early 2000s. Many HIV patients are likely to have suffered from STI and to have been treated with ciprofloxacin while having at the same time untreated TB. In this case, the lower dosage to treat STI would have increased the chance of resistance before any TB treatment had yet started. It goes without

saying that defaulting among MDR patients treated with second line treatment is likely to be a major cause of XDR. Default is likely to be higher for second line drugs compared to first line drugs because of higher frequency and severity of side effects, longer period of treatment, and the need to come back to King George, the referral hospital for second line treatment, which is far from where most patients live.

Other likely contributing factor to both MDR and XDR is the coexistence of TB and HIV/AIDS. The MDR and XDR were mostly diagnosed among inpatients and almost all of them were affected by HIV/AIDS. The fact that mortality was very high for both MDR and XDR suggests that these might have been terminal patients. It is urgent that each new TB patient in the district of Umzinythi is tested for CD4 and a plan on when to start ARV decided accordingly. The follow up of the survival of susceptible and resistant patients according to initial CD4 levels and coverage of ARV will indicate if mortality can be prevented by integrating ARV at a time when the CD4 have not declined to critical low levels.

The extent of the transmission to the general population is not known yet. The low prevalence of XDR and MDR among the contacts suggests a low transmission rate, which should be confirmed by re-testing the contacts in 2007.

The surveillance needs to be expanded to the whole TB population and not be limited to MDR and XDR cases. Any new TB case diagnosed in the district hospitals of Umzinyathi should have a culture specimen, to correctly categorize and treat each patient since the initial enrollment in the TB programme. This will allow to confirm if the situation found at COSH reflects the tip of the iceberg of a more generalized antibiotic resistance that is complicated by the interaction with HIV/AIDS.

The information coming from the surveillance should contribute to build the operational guidelines on how to contain the resistance. This can be done by expanding the scope of the surveillance from updating the XDR and the MDR cases to monitoring the TB control programme. This is the only way to know if the activities are implemented according to guidelines and if they are effectively reducing the development of resistance among poorly treated TB patients and the transmission from cases to susceptible contacts. This will allow to update the status of defaulters to improve their tracing.

A major outcome of the analysis of the information collected through the expanded surveillance will be an assessment of feasibility, costs and effectiveness of the proposed strategies. As with any effective intervention, also TB treatment is characterized by a critical gap between “what” to do and “how” to do it with available or extra resources. The cost-effectiveness of TB treatment has resulted in complacency, because it has been taken for granted that the guidelines were feasible. High rates of compliance in developed countries are characterized by relatively few patients per doctor and nurse. This is not the case when the guidelines are applied in countries affected by high prevalence of HIV/AIDS with subsequent staff overload. This situation has deteriorated even further because many assumptions have not been checked through a proper monitoring and evaluation system. Such systems are given a low priority in many TB control programmes, even if the guidelines propose otherwise.
The above situation has inevitably increased the antiobiotic resistance, reducing the initial cost

effectiveness of TB treatment because of the higher costs in treating resistant patients. The guidelines provide directions on "what to do" in terms of isolating inpatients, testing contacts, tracing defaulters and transferring patients to referral hospitals. The information gap is "how" to implement the guidelines without overloading the system.

This Issue of the Epidemiology Bulletin proposes to provide a district (Umzinyathi) with the technical assistance to set up a surveillance system with in- built monitoring and evaluation of the TB control programme. This will be possible by expanding the surveillance of the MDR and XDR cases and their contacts to the whole district of Umzinyathi and by integrating a monitoring system that will provide updated information on:
- the new and retreated TB cases,
- problems involved in isolating the inpatients,
- defaulters' tracing and the reasons for failing to trace them,
- progress in filling the staff positions,
- reduction of the waiting list in the referral system and
- other indicators.

Expanding the role of the surveillance system to monitor what is going on in the TB programme should increase the knowledge on why many assumptions do not work and what is required to make them feasible and cost effective.

The following areas will be critical for the surveillance system:

- Standardized data collection in the other district hospitals of Umzinyathi. Several sampling techniques were used at COSH in 2005 and 2006 and at the moment it is not clear if all the TB inpatients are systematically submitted to culture. The variation in the selection of the inpatients to be tested creates lack of comparability across hospitals and time periods, impairing the measurement of trends and the evaluation of the impact of the containment strategies. More than the type of selection, it is critical to ensure that whatever patient group is selected, the criteria are written down and applied consistently. Selecting OPD patients would certainly give a good proxy of the extent of the problem outside the hospitals but the sample would be too big to have sufficient power to capture the low prevalence existing in this group. Selecting each inpatient of the TB wards in the other district hospitals of Umzinyathi would help to estimate the prevalence in the most a risk population and would allow comparability with the data collected at COSH.

- Strengthened laboratory capacity. The increasing number of culture specimens requires faster techniques that can be transferred to the district level by providing equipment and training of local lab technicians. The quality assurance will be obtained by systematically sending a representative sample to the provincial lab to assess the reliability of the diagnosis carried out in the district laboratory.

- The expanded surveillance system should monitor and evaluate the feasibility, costs and effectiveness of the proposed strategies. The link between available human and other resources and the feasibility of maintaining efficiency and effectiveness are critical to produce the expected results. It is therefore insufficient to state that patients waiting for the culture results should be isolated if this is not accompanied by criteria about how

isolation could be done with available or extra resources. Strategies to be validated could include transferring cases to less utilized hospitals where unutilized wards could be re-converted into isolation wards and where ventilation should be increased. However, also in this case, having extra space will be insufficient without solving the problem of increasing the incentives to attract the staff in far way health units. The same goes with the updating of the daily number of defaulters and the provision of the conditions for tracing and convincing them to comply. The lack of follow up of the patients who are transferred to King George and other referral hospitals requires an effective communication link between hospitals.

- Operationalized guidelines. The aim of the analysis is to identify the critical mix of human and other resources required to maintain the efficient conditions for an effective coverage of a target population. This requires estimation of what needs to be put in place to maintain the efficiency of the system without reaching a point of diminishing returns. Any evidence based medicine intervention can become ineffective if the system is overstretched beyond a certain absorption capacity. The analysis of the data collected through the expanded surveillance should identify what is the maximum number of XDR, MDR and non-resistant TB patients per staff to maintain effectiveness. If higher numbers of XDR and MDR are to be covered, extra resources will have to be estimated to maintain a reasonable patient staff ratio that will not overload the system. Sensitivity analysis will strengthen the robustness of the results for wider extrapolation of the guidelines to other settings.

## Background

MDR and XDR define respectively the resistance of the mycobacterium tuberculosis to isoniazid and rifampicin (first line drugs) and to at least two second line drugs. The latest prevalence of MDR for KZN was measured in 2000-02, when 1.7% of new and 7.7% of retreated TB patients was found resistant to rifampicin and isoniazid. The information on the prevalence of XDR is limited because although it has been present in KZN it was never measured province wide. Dr Moll from Church of Scotland Hospital (COSH) started investigating why AIDS patients who were treated with ARV were dying from TB and found that they were resistance to at list two of the second line drugs. A more systematic testing was carried between January and May 2005 when cultures were taken according to the SA guidelines. A point prevalence survey was carried out on the 7th of February 2005 when all inpatients in the TB wards of COSH were submitted to culture. Since June 2005, besides the inpatients, also the outpatients suffering from signs and symptoms of TB have been submitted to culture. These statistics were presented at the last AIDS conference in September 2006 in Toronto and were published on the Lancet in October 2006. Since then, WHO, CDC and other international agencies had several meetings to discuss how to contain and prevent the spread of XDR, particularly in high HIV prevalence areas. WHO and its partners have organized task forces to deal with several aspects of XDR including:

- Definition of the cases suspected of being XDR;
- Definition of treatment guidelines;
- Laboratory case definition;
- Guidelines for health facility infection control;
- Guidelines for rapid surveys to determine XDR prevalence;
- Guidelines on communication strategies

This Issue of the Epidemiology Bulletin updates the status of the epidemic till the end of 2006 and suggests the next steps for its surveillance and containment. The analysis is based on the data collected at COSH, King George and other hospitals, to update the estimates of MDR and XDR and to build hypotheses on how the epidemic started and how it should be contained. The surveillance should have an epidemiological and a management focus to monitor the implementation of the guidelines. The Issue is divided into background, introduction, methodology, results, discussion and way forward, and conclusions.

## Introduction

The first clarification should be on the terminology. An epidemic outbreak is the unexpected increase in the number of cases that is limited in place and time. This term is applied to a variety of diseases differing in the speed with which they spread and cause mortality. Some outbreaks like Ebola and Lassa fever are characterized by such a high virulence that most if not all infected cases develop severe symptoms and die in a short time. This allows to identify and isolate cases and contacts and therefore limit the transmission also because the high mortality self limits the spread of the outbreak. Other infectious diseases like cholera are more known as epidemics because they can begin as limited outbreaks but then expand to wide geographic areas and last for a long time. This is facilitated by the fact that only a relatively small proportion of infected cases develop classic symptoms, allowing the initial outbreak to expand before the chain of transmission can be broken. Endemic diseases such as malaria in the northeast of KwaZulu-Natal become epidemics if the reported cases exceed the seasonal numbers reported in the previous years. Outbreaks and epidemics are dealt by isolating infective cases and contacts, and by treating the sources of transmission (e.g. food, water).

The second clarification is that the XDR is different from the classic outbreak, which results from increased transmission of bacteria and viruses from infected cases to susceptible individuals at a closed institution. As in any antibiotic resistance, the initial cases of MDR and XDR are likely to have resulted from treatment of already infected cases that then developed resistance. At the moment it is not known the extent to which these initial cases spread the infection of mutant bacteria to susceptible individuals. When Dr Moll and others investigated why AIDS patients were dying from TB, they started testing them for culture, and an unexpected number was found resistant. Because of the frequent coexistence of HIV/AIDS and TB, resistance could have developed in these patients before they reached COSH, which could have been the place of diagnosis and not the origin of the outbreak.

This is suggested by the seasonal pattern of the number of XDR cases and by the low infection rate among the family contacts. If a very short incubation period is excluded, the increasing XDR cases diagnosed in winter and the decreasing number in summer does not suggest the most XDR was hospital transmitted. This seasonal pattern is likely to reflect higher rates of hospitalization in winter and therefore increasing numbers admitted in the hospitals as already affected by AIDS and XDR. If this were the case, the term XDR outbreak should indicate more the place of diagnosis than the location where the XDR originated. At the moment it is therefore more likely that XDR is concentrated among terminal AIDS patients, although some transmission from these groups to other inpatients has likely occurred. The low infection rate among the family contacts seems to suggest that also the transmission to the general population has been limited. If this were the case, containment strategies would still have a high probability of containing the spread of XDR to the general population. It is likely that XDR will follow the same fate of the MDR, which started as a new phenomenon and is now a routine indicator of the performance of the TB treatment protocol.

The third clarification should be on the data sources. In the case of antibiotic resistance, such as the MDR or XDR, the passive notification of the TB programme is unlikely to capture the extent of the epidemic. The first cause of AIDS mortality in hospitals is TB and there is not much

incentive to test terminal patients. This situation does not allow to compare the statistics from COSH with that one coming from other hospitals. This explains why the number of XDR cases reported in KZN in 2005 and 2006 is much lower than at COSH. The much lower numbers reported through the routine system is likely to reflect under diagnosis in the other hospitals. Only by expanding the same proactive approach to other hospitals will tell if COSH is the tip of the iceberg of a more widespread resistance.

The spread of XDR is likely to have originated from many causes. MDR results from the poor implementation of TB treatment guidelines because rifampicin and isoniazid (first line antibiotics) are specifically used for TB. Development of XDR might not have had the same direct link to poor compliance with MDR guidelines. Kanamycin and ciprofloxacin (second line antibiotics) are used for other infectious diseases, and this might have created resistance across bacteria. Resistance of gonorrhea to ciprofloxacin was already known from the early 2000s and it is likely that HIV patients suffering from gonorrhea and initial TB re-activation might have been treated before any TB treatment started. The lower dosage used for STI in a patient with concomitant untreated TB is likely to have created resistance of mycobacterium to ciprofloxacin. This does not exclude that resistance can also have derived from MDR cases that were still sensitive to second line drugs but defaulted. After being transferred to King George referral hospital, MDR patients were discharged after a few months with the assumption that they would have come back monthly to refill their drug supply. The distance from King George, the long time required to complete the treatment, the side effects and the absence of a tracing system caused defaulting and therefore XDR.

The objective of this analysis was to update the situation till December 2006 and to set up the next steps for the surveillance. The available data sources were reviewed and the cases were classified according to the latest XDR definition. The description of the epidemic in place and time provided the basis for the hypotheses on the origin of the epidemic and the requirements for its containment.

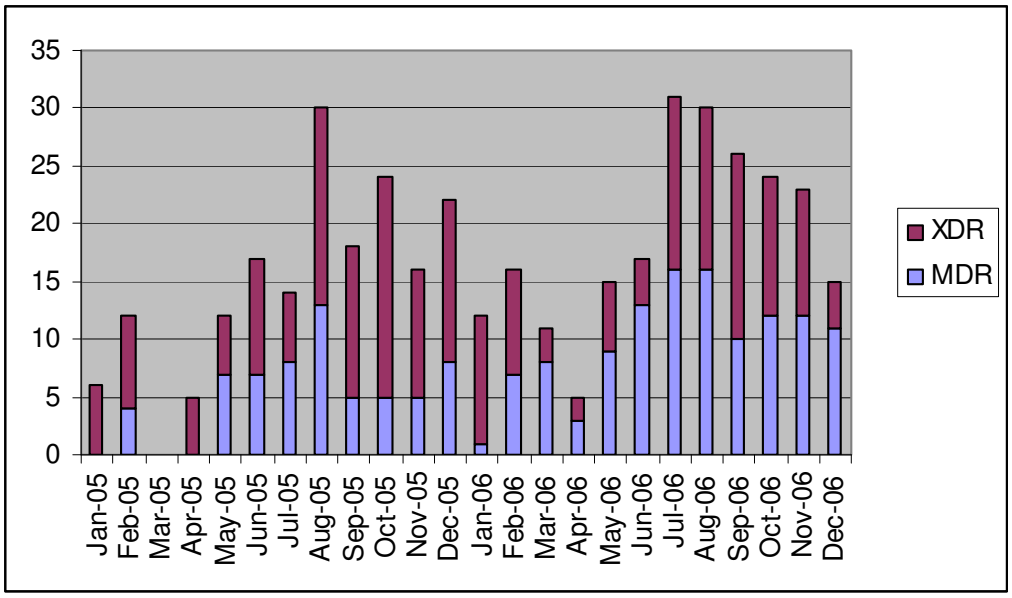
**Methodology**

The Italian Cooperation, which was already supporting the management team of Umzinyathi district, offered technical assistance to review the data collected at COSH. Since October 2006, two research assistants from the Italian Cooperation were stationed at COSH to review the organization, strengths and weaknesses of the data sources. The first step was to review the information collected at COSH between 2005 and 2006 on the MDR and XDR cases and the contacts. The tracing teams were provided with GPS to collect the coordinates of the households of the MDR and XDR cases identified from October 2006 onwards. The data on the patients transferred were obtained from King George. MDR was defined as resistant to isoniazid and rifampicin, and XDR was defined as extra resistance to ciprofloxacin and kanamycin, because these were the second line antibiotic measured at COSH. Data were analyzed through SPSS 14 to update the situation and build hypotheses on the origin and spread of the epidemic.

## Results

Between January 2005 and December 2006, COSH recorded 180 MDR and 221 XDR cases. MDR cases were categorized as resistant to rifampicin and isoniazid (first line), while XDR cases had the extra resistance to kanamycin and ciprofloxacin (second line). Figure 1 shows that the number of MDR and XDR cases were lower in summer and increased in winter, reflecting the seasonality of hospitalization. As the active diagnosis was mainly carried out on inpatients, the increasing hospitalization in the colder season provided a higher number of diagnoses. On the other side, a greater number of hospitalized patients without proper isolation and ventilation are likely to have created a high risk of transmitting XDR to other inpatients.

**Figure 1 Number of XDR and MDR cases per month at COSH**




The age pattern of MDR cases differed from that one on the XDR cases. Figure 2 shows that the age and gender distribution of MDR cases reflects the TB profile, with more males being represented with similar age pattern between males and females. Figure 3 shows that the XDR age and gender distribution reflects the typical pattern of HIV/AIDS, with females getting infected at a younger age than males. Figure 4 shows that while males had a higher overall number of MDR/XDR cases, females had a significantly higher number of XDR cases. This association was statistically significant but it might have been caused by the variation in the selection criteria. The lack of standardization is suggested by the high monthly variation in the number of MDR and XDR among males and females (Figure 5), which is likely to be due to the inconsistent application of the inclusion criteria for culture test.

**Figure 2 Age groups of MDR cases, COSH 2005-06**

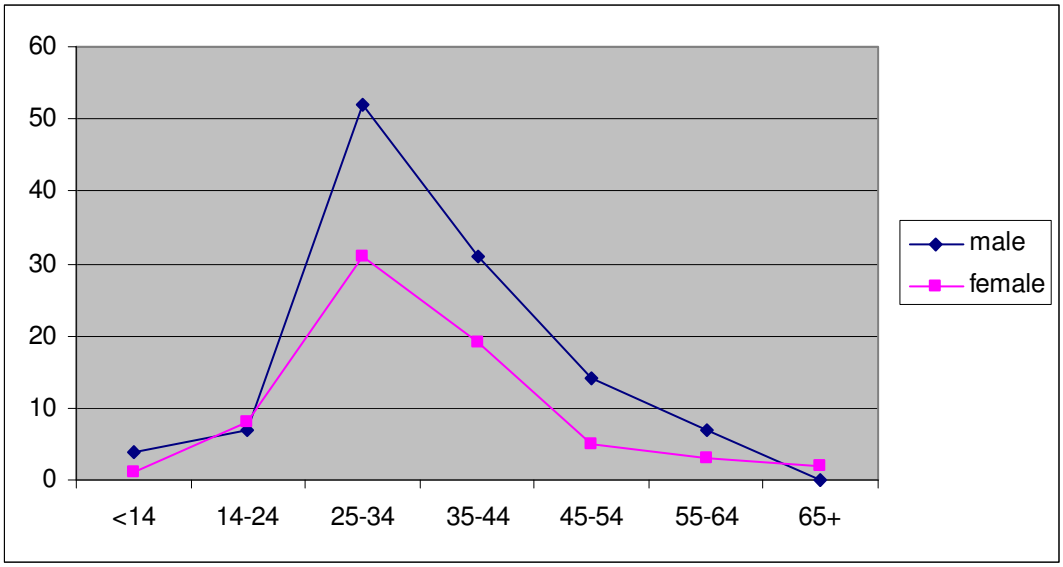



**Figure 3 Age groups of XDR cases, COSH 2005-06**

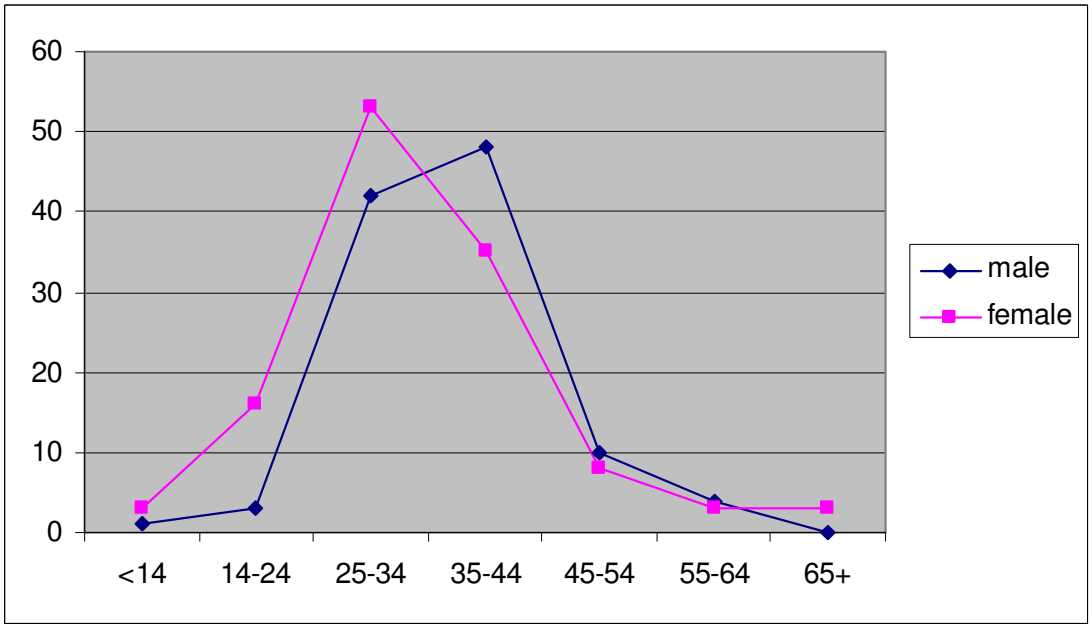


**Figure 4 MDR and XDR gender distribution**

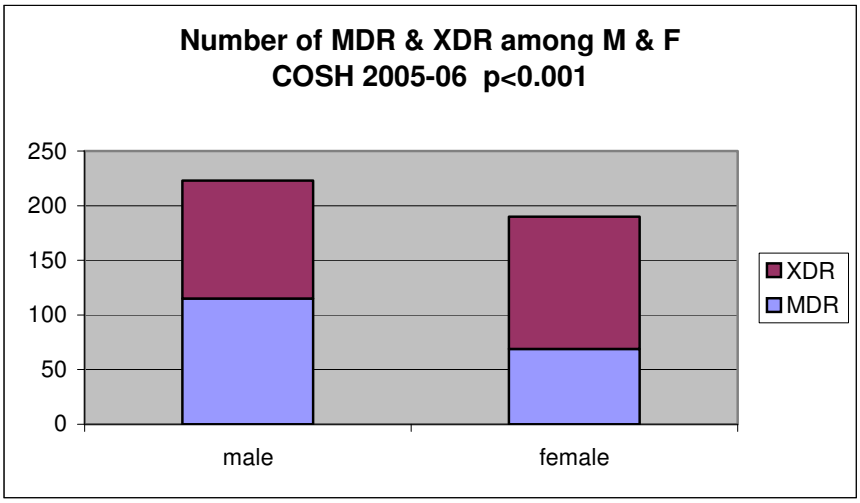
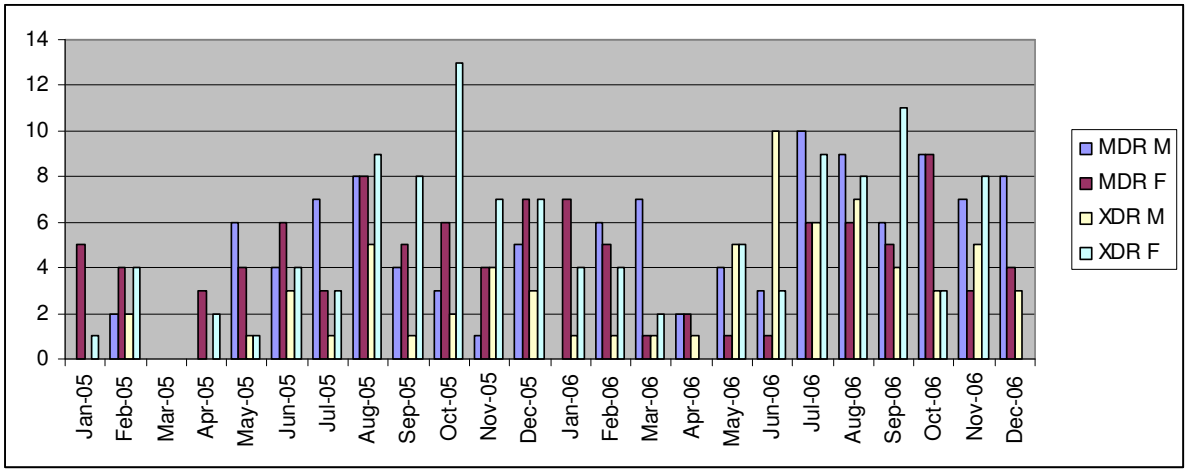



**Figure 5 Distribution of MDR and XDR cases per month, males and females**

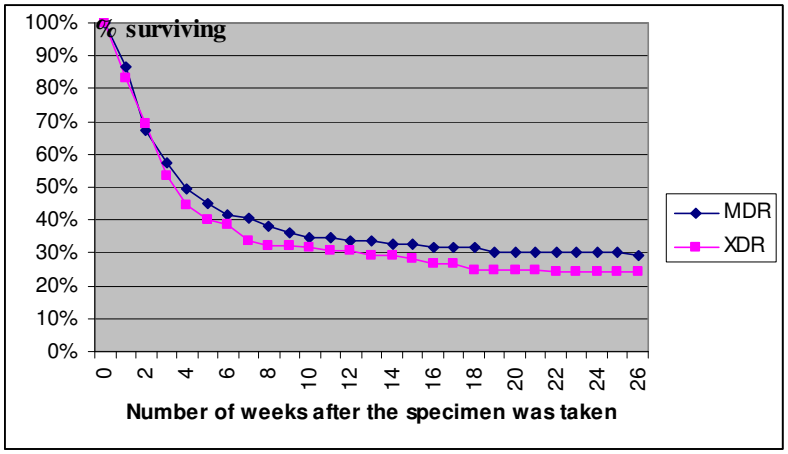



Six-month mortality was estimated for the cohort of patients that were diagnosed between the 1st of January 2005 and the 30th of June 2006. Of the total patients, 157 MDR and 175 XDR cases had valid dates of specimen collection and outcome, and each case provided the same follow up period, whatever the date of entry into the follow up. The first case diagnosed in January 2005 contributed for the period up to June 2005, while the last case diagnosed in June 2006 contributed up to the end of December 2006. Death which occurred after the first six month were not considered, for example if a patient was diagnosed in January 2005 and survived up to June 2005 was considered a survivor, even if the same patient died soon afterwards.

Figure 6 shows that the mortality was steepest during the first three weeks, declined between the fourth and the seventh weeks and continued at a slower pace afterwards. The Y axis shows the proportion of MDR and XDR cases remaining alive at the end of each week following the specimen. The steep mortality of the first two weeks was followed by a slight decline, which continued till the 7th week, after which mortality slowed down. By the end of the first six months only 29% of MDR and 24% of XDR were still alive.

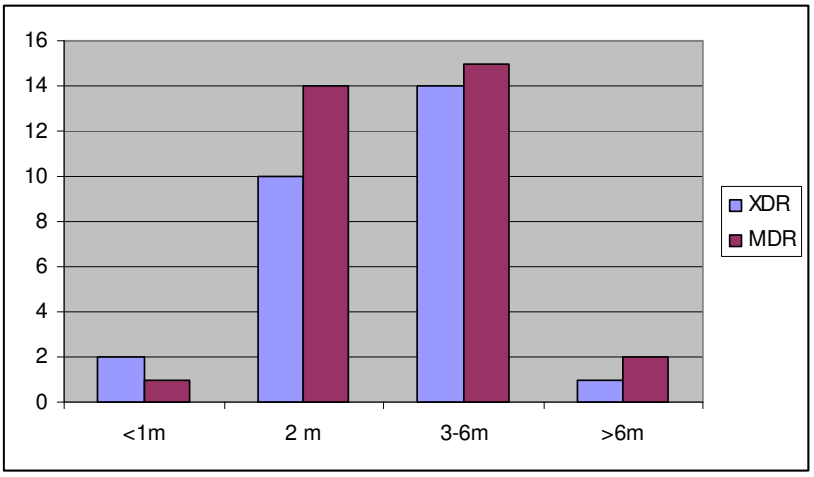
The initial steep mortality and the fact the survival curve did not differ significantly between MDR and XDR cases suggests that most of these patients were probably terminal AIDS patients. These conditions might have resulted in high mortality whatever TB strain these patients were infected with. The surveillance system should check if the same low survival might be present in HIV/AIDS patients affected by non-resistant TB. If this were confirmed, the only way to decrease mortality would be to start ARV as soon as possible when patients are diagnosed with levels of CD4 that are associated with re-activation of TB. It would be also critical to measure the mortality of MDR and XDR cases that are not HIV positive. The surveillance will be able to measure the incremental cost-effectiveness associated with a stronger integration between the ARV and TB treatment.

**Figure 6 Six-month survival of the cohort diagnosed between 1/1/05 and 30/6/06**




Only a small proportion of XDR cases reached King George. Only 30 cases were transferred to King George, of whom 6 died before discharge. Of the 24 XDR cases who were discharged and followed up as outpatients, 17 have died, 4 were still alive and 9 had unknown outcome by the end of 2006. The low proportion of XDR cases being transferred is related to high mortality and waiting list. Most patients died before the results of the culture came back, while the rest had to wait because of the high occupancy of King George. Figure 7 shows the time between the date when the specimen was taken and the date when the 30 patients were transferred to King George. While two months was the time required for the results of the culture test, a longer waiting time was related to the shortage of space at King George. These past practices are likely to change with the opening of the new referral hospital at Greytown but the waiting list is unlikely to disappear.

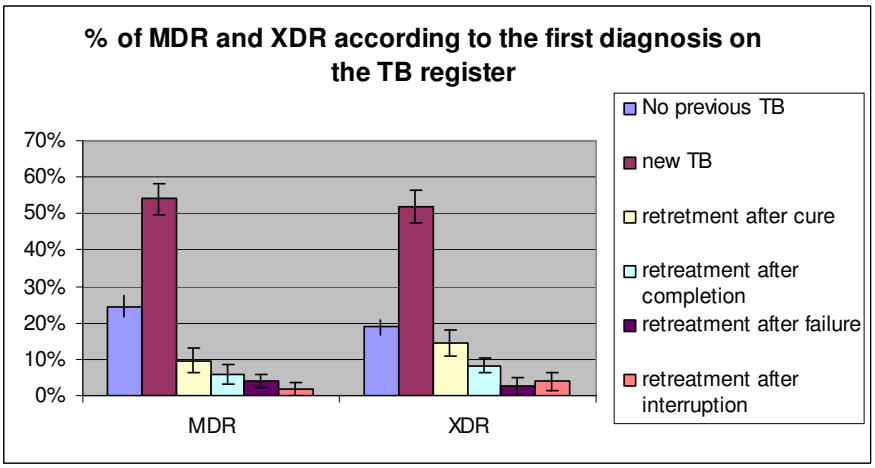
**Figure 7 Time lag between culture taking and admission to King George (UPDATE)**




*Previous history of TB*

The names of the MDR and XDR cases were traced on the paper TB register of the DOT office of COSH to identify if they had a previous history of TB treatment. About 25% of MDR and 19% of the XDR were not recorded on the TB register, 54% of MDR and 52% of XDR had been previously treated as new TB cases, while 21% of MDR and 29% of XDR were retreated TB cases (Figure 8). Except for the retreated cases, no firm conclusion can be drawn on the previous history of TB, because any new TB case that was treated in the past according to the smear test might have been already infected with resistance strains, which however might have been diagnosed after several months. Only a longitudinal study could investigate on the association between previous TB treatment and development of MDR and XDR.

**Figure 8 Previous history of TB between XDR and MDR**



## Discussion

The above data suggest the need (a) to standardize the inclusion criteria for submitting patients to culture and (b) to monitor the implementation of the proposed containment strategies proposed by WHO.

*Standardized inclusion criteria*

Inclusion criteria should be applied consistently in the surveillance system. The data collected between different time periods need to be comparable to reliably estimate trends and impact of containment strategies. The population groups selected since January 2005 included: (a) consecutive patients not responding to treatment; (b) all inpatients on a single day in February 2005; and (c) consecutive inpatients and outpatients with symptoms of TB. These different population groups, which were sampled to get the culture specimens on which to base the prevalence, might have introduced a certain selection bias. For example the spike for February 2005 in Figure 2 is related to the point prevalence carried out on a single day of February 2005, while no XDR case was reported the following month. Because the monthly numbers are relatively small, lack of standardization can produce wide monthly fluctuations. When these variations add up, they can produce a false decrease or increase between years, impairing conclusions about impact of containment. Standardization should produce better estimates of prevalence, incidence and mortality of XDR and MDR. Once it has been decided that each admitted patient in the TB wards are to be submitted to culture, or whatever alternative criteria is decided, this should be applied consistently.

The feasibility of expanding the same inclusion criteria to the other hospitals of Umzinyathi should be tested. The much lower number of MDR and XDR cases reported by the other district hospitals is likely to reflect the more lax criteria about who is presently submitted to culture in other hospitals besides COSH. To be able to compare statistics across hospitals it will be necessary to apply the same inclusion criteria across all the hospitals of Umzinyathi to estimate the district prevalence of XDR.

*Operational guidelines*

Another major outcome of the surveillance would be the testing and evaluation of guidelines. This includes: (a) decreasing hospital transmission through transferring suspect XDR cases to less utilized hospitals, where unutilized wards could be re-converted into isolation wards, and by increasing the ventilation; (b) decreasing defaulting by producing timely updates of names to be given to the tracing teams; (c) creating stronger communication links between district and referral hospitals; (d) monitoring the effectiveness of implementation; and (e) using the experience to inform the production of operational guidelines.

*Expansion of surveillance*

Being XDR the result of poor compliance, it would be self-defeating to focus on the XDR only. All non-resistant TB patients, MDR and XDR cases should be followed up longitudinally through an expanded TB register and a more organized data collection system. This longitudinal

follow up of each TB patient and of the programme's activities will allow to reply to the questions under study. The recording of the information related to XDR, MDR, contacts, suspect cases, new and retreated TB patients will be analysed to estimate seasonal patterns, characteristics of the patients, risk for defaulting, factors influencing efficiency, cost and effectiveness of containing XDR. This will help to understand the problems affecting the overall management of the TB programme and how these problems could be tackled through a more feasible and effective use of available and extra resources.

The population should include any XDR, MDR and TB patient presently under treatment or who will be diagnosed in 2007 in Umzinyathi district. The place of operation should be the district administrative capital Dundee, where an itinerant team will be based to coordinate the data collection in hospitals and clinics. Each district hospital should have a data clerk trained in collecting data on the new and retreated TB, MDR and XDR, defaulters, contacts, culture results and other data available from the TB and DOT registers. The itinerant team will visit at regular intervals the clinics and the hospitals of Umzinyathi to update the data and send the file to the district manager and the epidemiology Unit of the DOH. These will be entered into a database to produce monthly reports and carry out more sophisticated analysis on the indicators related to the activities, patients and outcomes to monitor effectiveness of strategies.

*Referral system*

As previously mentioned, the inpatients in the TB wards will be submitted to culture and if they will be confirmed MDR or XDR they will be transferred to King George and the new referral hospital in Greytown. Because there is a risk that the patients are lost after they are discharged from King George or Greytown, each district hospital needs to establish an effective communication channel between district and referral hospitals. Once a transfer occurs, the data clerk at each district hospital should enter the expected date of discharge into a database. At the date of discharge, the software will produce automatic reminders to contact the referral hospitals to confirm if the patients have returned to Umzinyathi. These names should be provided to the tracing ream so that they will be brought back to the DOT office to start the monthly visits. The feasibility of allowing district hospitals to distribute second line drugs after the discharge from the referral hospitals will be monitored to identify problems in implementing standardized protocols. This will help to define accreditation procedures for the management of XDR cases at district hospitals.

*Contacts of MDR & XDR*

The data clerk at the district hospitals should collect the data related to the contacts. Once a patient is diagnosed as MDR or XDR, the tracing teams will continue to locate the households to take the GPS coordinates and to bring them to the DOT office. They will be submitted to culture and other tests and the data clerks will enter the information into the database and will update the results when they will come back. Due to the shortage of the tracing teams and the limited absorption capacity of the laboratory at Durban only the household members of MDR and XDR cases are presently being traced. The inclusion of other contacts outside the family members should be included in case they are likely to spread transmission (e.g. teachers).

*Record keeping*

The data clerk and the itinerant team will have the function of ensuring a more organized data storage than it is at the moment. The surveillance system is a sort of an expanded TB management information system with the objective of checking if the activities are running as planned. At the moment information is scattered on paper forms including several registers kept by the DOT Office on XDR and MDR cases and their contacts. The information from these records will be organized into a database to retrieve individual records and to produce tables and graphs on indicators. The tracing teams will collect the GPS coordinates, which will be used by the GIS Unit to put the XDR and MDR cases on the map to identify the spread of transmission and to improve efficiency in tracing defaulters.

The surveillance should include management issues to improve the treatment of all TB patients. All TB patients are recorded on the TB paper register and the next appointments are written down on a paper diary, which should be transformed in electronic format. The appointment diary could be more efficiently used if the data are entered into a database, which will have the name of each patient on each row and the date of registration (first visit) on the first column. At the second visit, the nurse will enter the date, which will be updated at each monthly visit. If a patient does not come as scheduled for the second visit, no date will be entered and the internal clock of the computer will produce a reminder related to those patients exceeding more than 30 calendar days from the last valid date. At the end of each day, the database will produce a list of defaulters who will be traced by the tracing teams to bring them back to the DOT Office. The system will be tested in terms of feasibility costs and effectiveness in reducing the defaulters compared with the paper dairy.

The suspect for TB should be also recorded into the database. The OPD patients are usually asked if they had been coughing continuously in the previous two weeks (suspect for TB) and if they had, sputa are collected to carry out smear diagnoses. OPD patients who spontaneously complain about symptoms related to TB are submitted to the diagnostic procedure according to the TB guidelines. Those who are diagnosed with TB will continue to be recorded on the TB register and on the database related to the registration date and the follow up dates.

Hospital management will provide the information related to infrastructure, staff, CHWs, volunteers, transport, drugs' consumption, laboratory tests and other consumables that will be quantified and costed. The information will be used to identify various strategies where different interactions between inputs, outputs and outcomes will influence costs and effectiveness.

It is too early to expand the data collection to other indicators without first checking the feasibility of collecting the priority information mentioned above, but as the situation will evolve other data sources will be traced. Some of these data sources include the hospital and OPD records which at the moment are on paper format and could be entered into a database to estimate impact of strategies on hospitalization rates in the TB wards. Extra data collection could include task analysis to measure the burden on the staff and how it affects the compliance with guidelines, exit interview of OPD patients to assess quality of services, household surveys of defaulters and CHW interviews.

*Data handling and analysis*

The Italian Cooperation, the Epidemiology Unit and the GIS Unit of the DOH will analyze the data to monitor the epidemic and to identify the most feasible and cost-effective containment strategies. The information will be entered into a database that will be programmed to extract tables and graphs to monitor the epidemic and to export the files for further analysis. The GIS Unit will update the maps to follow up the special progression of the epidemic and identify clusters of cases. The indicators will be related to estimate the coverage of the contacts, process indicators and progress in the completion of treatment, default death and cure rate.

*Users*

The expanded surveillance will alert the district management and the clinical staff of the progress in the containment of the epidemic. This will include description of the cases in place and time, identification of impending problems such as increasing number of defaulters requiring tracing, location of the most affected areas requiring strengthening of efforts and updating of the treatment indicators. Monitoring of diagnoses, activities and outcomes will be critical to check the effectiveness of the containment strategies. This will help to build guidelines to investigate and contain XDR in other settings.

*Time schedule*

The surveillance system will be gradually expanded in 2007 and 2008. After 2008, the data collection will be integrated within the mainstream management of the TB control programme. This will allow sufficient time to follow up the cohort of patients already under treatment and the new case that will be enrolled in 2007 and will be followed up longitudinally to assess the impact of control activities.

*Risks*

The success of the surveillance depends on the commitment of several people. The staff from the Italian Cooperation will continue to support the staff at COSH to improve the results of their information efforts. The DOT nurses should not have many problems in shifting from the paper diary to the database to keep track of appointments to produce a daily list of those who did not come as scheduled. The tracing team should not have problems in spending a few minutes to take the GPS coordinates, which will be at their own advantage when they have to locate the defaulters. There is a need to keep track of the XDR patients after they are discharged from King George and this can be arranged through proper channels. As usual, the devil is in the details and the experience that will be built in 2007 and 2008 will help to fine-tune the protocols for a smoothly run surveillance system.

**Conclusions**

The final goal is to understand how the XDR epidemic is evolving and how it can be contained through better management of the TB control programme. The first results will be a description in time and place of the XDR and MDR cases, the hypothesis testing about the origin of the epidemic and the best options to control its spread. The analysis will identify factors associated with compliance, constraints in implementing the TB guidelines and the added value of alternative strategies. If XDR is the result of poor implementation of normal TB control, it is time to check why existing guidelines are not working and to monitor what can be done, how and at what costs. The data should be analyzed to identify the conditions of effectiveness, without which efficiency declines to a point when evidence based treatment does not work. This will help to fill the gap between "what" works in ideal conditions and "how" it could work in operational conditions. This is the condition *sine qua non* to build operational guidelines that can be based on quantification of the inputs, outputs and outcomes, costs, facilitating and impairing circumstance influencing efficiency and effectiveness in covering a catchment population.

This should strengthen the effectiveness of the control strategies in decreasing the transmission of XDR to the general population and in reducing resistance among those already under treatment. The information collected through surveillance will be used to identify and isolate the cases in place and time, and to effectively mobilize available resources to implement feasible and cost effective alternatives to control the epidemic. The district authorities will benefit from reducing the epidemic and the provincial authority will benefit from using the information to apply the strategies to other districts. The surveillance will be critical to reply to several questions including: are XDR increasing in other areas of Umzinyathi ? Are XDR cases concentrated among AIDS patients and can the interaction with ARV reduce the number of XDR cases ? Are XDR cases transmitting the infections to the general population ? What can be done in terms of control strategies with available resources ?

The sustainability is ensured by the fact that the Italian Cooperation is providing help on how to use local resources and by adding a few human resources that will be trained to perform specialized tasks. These extra staff will be gradually integrated into the district system while the DOH will continue to provide the support through the GIS Unit to assist in GIS mapping and in the database programming. The provincial laboratory of Albert Luthuli is the only one with specialized skills and equipment but it is hoped that decentralization to the district will follow.

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